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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/447,218 | 11/23/1999 | A.K. GUNNAR ABERG | 4821-362 | 3537 |

20583 7590 05/15/2006

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| EXAMINER | |
|---|---|
| CHANG, CELIA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

DATE MAILED: 05/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/447,218 | ABERG ET AL. | |
| | Examiner | Art Unit | |
| | Celia Chang | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *34,39,40 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,39,40 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

**1.** This is a RCE of SN 09/447,218.

The claims filed by applicants in an after final amendment have been entered per applicants' request.

Claims 1-33, 35-38, 41-50 have been canceled.

Claims 34, 39-40, 51 are pending.

**2.** Applicant's arguments with respect to claims 34, 39-40, 51 have been considered but are moot in view of the new grounds of rejection.

**3.** Claims 34, 39-40, 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what is the scope of claims 34, 39-40 or 51 because the claims are drawn to administering a "therapeutically effective amount" wherein the amount is 5 mg per day. Is this a single effective dose? Is this a multiple effective dose but with a cumulative effect of 5 mg per day? Is this Descarboethoxyloratadine externally administered? Or is this descarboethoxyloratadine *in situ* generated? Please note that the "therapeutically effective" dose wherein the amount is 5 mg per day may encompass all of the scenario as described supra in absence of any particularity as required by the second paragraph.

**4.** Claims 34, 39-40, 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification lacks antecedent basis for the scope of treating urticaria comprises 5 mg, or "adapted for administration in a single dose per day".

A survey of the specification indicated the following:

On page 14, lines 27-28 it was described "*The term "therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof" is encompassed by the above described dosage amounts*"

On page 14, lines 10-17, it was described "*In general, the total daily dose range for the conditions described herein is from about **0.1 mg to thess than about 10 mg** administered in single or divided doses orally, topically, transdermally or locally by inhalation. For example, a preferred oral daily dose range should be about **0.1 mg to about 5 mg**. A more preferred oral dose is about **0.2 mg to about 1 mg**.*

On page 28, examples 7-9 disclosed unit dosage capsules, soft gelatin capsules and tablets containing ***dosage unit** of 0.1 to 10 milligram.*

In view of the above disclosure, it was clear that the preferred range and the unit dosage range does not contain any single dosage description nor any single dosage per day description. In the description above nowhere can the one single dose of 5 mg as a single effective dose or in a unit dosage composition was found. As a matter of fact from the more preferred oral dose as disclosed on page 14, line 17, the narrower range is 0.2 mg to 1 mg which would not provide a "blaze mark" on 5 mg since it is at the high end of the preferred range. As set forth by the decision remarked by applicants in Fujikawa v Wattanasin, the Examiner has looked for blaze marks which single out particular trees but failed to see any.

**5.** Claims 34, 39-40, 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In view of the well recognized pharmacokinetic understanding in drug dosage regimens (see Notari et al. p.163-164), the specification as delineated supra would be considered guiding one skilled in the art to use multiple dosage units of the most preferred oral dose composition in units *about **0.2 mg to about 1 mg*** to achieve the required *daily dose range which should be about **0.1 mg to about 5 mg*** (the preferred oral dose range) which would be a teaching away from the instantly limitation of single dosage of 5 mg per unit dose. No where in the specification provided enablement for a single unit oral dosage form in 5 mg per unit dose with efficacy in

maintaining serum concentration as required by the above range of therapeutic values. Nor was there any "daily" single dose being enabled.

**6.** The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 34, 39-40, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atsushi et al. in view of Hilbert et al. CA 108:31237, Garattini supplemented by Clissold.

***Determination of the scope and content of the prior art ( MPEP §2141.01)***

Atsushi et al. disclosed clinical method for treating urticaria using a 10 mg once daily dose of loratadine.

***Ascertainment of the difference between the prior art and the claims ( MPEP §2141.02)***

The difference between the instant claims and the prior art is that instead of loratadine, the claims are drawn to the use of 5 mg per day descarboethoxyloratadine which is a metabolite of loratadine (CA 108:31237) i.e. a in situ generated active product and quantity of loratadine. Garattini taught that the active metabolite of a drug participates in the effect of the parent compound by sustaining the action over time. Clissold et al. disclosed that loratadine is extensively metabolized in humans (see p. 49 left column second paragraph) and there is about a 50% conversion to DLC upon oral administration of loratadine (see p. 47-48).

***Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)***

One having ordinary skill in the art in possession of the Atsushi et al. method is in possession of the claimed method because inherently, in treating urticaria using loratadine, the method of treating urticaria using descarboethoxyloratadine is being conducted. In the instant case, the Clissold et al. provided *factual evidence* that when plasma concentration of loratadine start to decrease due to metabolism, the active metabolite started to maintain its plasma level and

continued through the 24 hours or longer of duration which verified the general teaching well known in the art by Garattini that active metabolite contributes to the drug activity. Further, from the Cmax variation between the distribution of loratadine and DLC disclosed by Clissold et al. one having ordinary skill in the art recognized that at 1.5 hours, there is about a 50% conversion (see 10 mg oral dose at 1.5 hours 4.7 μg/ml loratadine and 4.0 μg/ml DLC 50/50 distribution, p.47-48). That is administering drug and administrating its active metabolite is identical since one is administering the precursor to form an active species i.e. the metabolite *in situ*, the other is administering *the* active species, i.e. metabolite which is also active. With the metabolite distribution, it is also within the skill of the artisan to know giving a 10 mg dose of loratadine would enable the dosage for DLC to be 5 mg i.e. 50% conversion.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 34, 39-40, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shareeah in view of Hilbert et al. CA 108:31237, Garattini supplemented by Clissold.

***Determination of the scope and content of the prior art ( MPEP §2141.01)***

Shareeah disclosed method of treating urticaria using a once daily 10 mg dose of loratadine.

***Ascertainment of the difference between the prior art and the claims ( MPEP §2141.02)***

The difference between the instant claims and the prior art is that instead of loratadine, the claims are drawn to the use of 5 mg per day descarboethoxyloratadine which is a metabolite of loratadine (CA 108:31237) i.e. a in situ generated active product and quantity of loratadine. Garattini taught that the active metabolite of a drug participates in the effect of the parent compound by sustaining the action over time. Clissold et al. disclosed that loratadine is extensively metabolized in humans (see p. 49 left column second paragraph) and there is about a 50% conversion to DLC upon oral administration of loratadine (see p. 47-48).

***Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)***

One having ordinary skill in the art in possession of the Shareeah method is in possession of the claimed method because inherently, in treating urticaria using loratadine, the method of treating urticaria using descarboethoxyloratadine is being conducted. Especially, it was clearly known by one having ordinary skill that the active metabolite at least is participating in the sustaining of action of the drug over time. In the instant case, the Clissold et al. provided *factual evidence* that when plasma concentration of loratadine start to decrease due to metabolism, the active metabolite started to maintain its plasma level and continued through the 24 hours or longer of duration which verified the general teaching well known in the art by Garattini that active metabolite contributes to the drug activity. Further, from the Cmax variation between the distribution of loratadine and DLC disclosed by Clissold et al. one having ordinary skill in the art recognized that at 1.5 hours, there is about a 50% conversion (see 10 mg oral dose at 1.5 hours 4.7 μg/ml loratadine and 4.0 μg/ml DLC 50/50 distribution, p.47-48). That is administering drug and administrating its active metabolite is identical since one is administering the precusor to form an active species i.e. the metabolite *in situ*, the other is administering *the* active species, i.e. metabolite which is also active. With the metabolite distribution, it is also within the skill of the artisan to know giving a 10 mg dose of loratadine would enable the dosage for DLC to be 5 mg i.e. 50% conversion.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie, Ph. D., can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*OACS/Chang*
*May 3, 2006*

*Celia Chang*
*Primary Examiner*
*Art Unit 1625*